

VERSION WITH MARKINGS TO SHOW CHANGES

On page 1 of the specification:

This application is a continuation application of serial no. 08/599,226, ~~filed on April 16, 1999, which is a continued prosecution application of serial no. 08/599,226~~, filed on February 9, 1996, pending issued as Patent No. 6,090,382. The contents of all of the aforementioned application(s) are hereby incorporated by reference

In the claims:

65. A method for inhibiting human TNF α activity comprising contacting human TNF α with an antibody such that human TNF α activity is inhibited, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNF α with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less.

66. A method for inhibiting human TNF α activity comprising contacting human TNF α with an antibody such that human TNF α activity is inhibited, wherein the antibody is an isolated human antibody, or antigen-binding portion thereof, with the following characteristics:

- a) dissociates from human TNF α with a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, as determined by surface plasmon resonance;
- b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;
- c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2,

3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

67. A method for inhibiting human TNF α activity comprising contacting human TNF α with an antibody such that human TNF α activity is inhibited, wherein the antibody is an isolated human antibody, or an antigen binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

68. A method for inhibiting human TNF α activity in a human subject suffering from a disorder in which TNF α activity is detrimental, comprising administering to the human subject an antibody such that human TNF α activity in the human subject is inhibited, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNF α with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC₅₀ of 1×10^{-7} M or less.

69. A method for inhibiting human TNF α activity in a human subject suffering from a disorder in which TNF α activity is detrimental, comprising administering to the human subject an antibody such that human TNF α activity in the human subject is inhibited, wherein the antibody is an isolated human antibody, or antigen-binding portion thereof, with the following characteristics:

- a) dissociates from human TNF α with a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, as determined by surface plasmon resonance;
- b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1,

4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

70. A method for inhibiting human TNF α activity in a human subject suffering from a disorder in which TNF α activity is detrimental, comprising administering to the human subject an antibody such that human TNF α activity in the human subject is inhibited, wherein the antibody is an isolated human antibody, or an antigen binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

71. **(Amended)** The method of claim 70, wherein the disorder is sepsis. A method for inhibiting human TNF α activity in a human subject suffering from a disorder in which TNF α activity is detrimental, comprising administering to the human subject an antibody such that human TNF α activity in the human subject is inhibited, wherein the antibody is D2E7.

73. **(Amended)** The method of any one of claims 68, 69, [claim] 70, or 71 wherein the disorder is an autoimmune disease.

76. **(Amended)** The method of any one of claims 68, 69, [claim] 70, or 71 wherein the disorder is an infectious disease.

77. **(Amended)** The method of any one of claims 68, 69, [claim] 70, or 71, wherein the disorder is transplant rejection or graft-versus-host disease.

78. **(Amended)** The method of any one of claims 68, 69, [claim] 70, or 71, wherein the disorder is a malignancy.

79. **(Amended)** The method of any one of claims 68, 69, [claim] 70, or 71, wherein the disorder is a pulmonary disorder.

80. **(Amended)** The method of any one of claims 68, 69, [claim] 70, or 71, wherein the disorder is an intestinal disorder.

81. **(Amended)** The method of any one of claims 68, 69, [claim] 70, or 71, wherein the disorder is a cardiac disorder.